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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Howard Bernstein, Donald Chickering, Sarwat Khattak and Julie Ann Straub	
Serial No:	09/255,179	Art Unit: 1617
Filed:	February 22, 1999	Examiner: E.Webman
For:	*Matrices Formed of Polymer and Hydrophobic Compounds for Use In Drug Delivery*	

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 35 U.S.C. 1.132

I, Howard Bernstein, hereby declare that:

1. I have a Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology and an M.D. from Harvard Medical School. I have conducted research in the area of microencapsulation for drug delivery and diagnostic imaging for approximately nineteen years. I am currently Sr. Vice President for Research and Development at Acusphere, Inc., in Cambridge, MA. My resume is attached.

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2. I am an inventor of the method and compositions described in the above identified U.S. patent application. I have read the office action mailed February 14, 2001.

3. U.S.S.N. 09/255,179 discloses both matrices formed of polymers, hydrophobic compounds and therapeutics having improved release of the therapeutic from the matrices and methods for producing these matrices. Microparticles disclosed in the patent application are different from the prior art microparticles. The prior art cited by the Examiner, U.S. Patent No. 5,855,913 to Hanes et al. discloses porous polymeric microparticles with hydrophobic compounds where the hydrophobic compound is used to prevent microparticle agglomeration. The porosity of the microparticles is created when the solvent used to dissolve the drug and polymer is removed.

4. In contrast, our application discloses microparticles in which the polymer, the hydrophobic compound and the therapeutic form porous microparticles where pore forming agents are used to create the porosity. The pore forming agents are added to the solution or emulsion of the drug, polymer and hydrophobic

compound prior to the microencapsulation process. The pore forming agent is removed during the microencapsulation process resulting in the formation of a porous matrix. The porous microparticles produced in this manner have drug release kinetics which could not have been predicted and which are significantly different from those of the prior art.

5. To further demonstrate the difference between the microparticles of Hanes, and those described and claimed in U.S.S.N. 09/255,179, we conducted the following comparative studies.

a. Microparticle Production

Three different batches of prednisone containing microparticles were produced using spray drying as described in Exhibit A. Poly(lactide co-glycolide) (PLGA 50:50) was selected as a representative biocompatible polymer. 1,2-Diarachidoyl-sn-glycero-3-phosphocholine (DAPC), a phospholipid was selected as a representative hydrophobic compound. Prednisone which is a steroid was selected as a representative drug. The first batch of prednisone microparticles (Lot 9919-163) was made from the

polymer PLGA without the hydrophobic compound DAPC and without using a pore forming agent during the microencapsulation process. The microparticles were produced by dissolving the PLGA and prednisone in an organic solvent, methylene chloride. This solution was then spray dried to remove the methylene chloride and to form the microparticles. The second batch of prednisone microparticles (Lot 9919-164) was made as disclosed in the Hanes patent. Prednisone, PLGA and the hydrophobic compound DAPC were all dissolved in methylene chloride. This solution was then spray dried to remove the methylene chloride as disclosed in Hanes. The third batch of prednisone microparticles (Lot 9919-166) was produced as disclosed in our patent application by dissolving the prednisone, PLGA and DAPC in methylene chloride. Ammonium bicarbonate (a volatile salt) was used as a pore forming agent. To the organic solution of prednisone, DAPC and PLGA, a solution of ammonium bicarbonate was added and the combination was then emulsified. The emulsion was spray dried to remove the methylene chloride and the ammonium bicarbonate to form the porous microparticles.

b. Measurement of Prednisone Release From the Microparticles

To assess the *in vitro* release kinetics of the three prednisone microparticle batches, the release of prednisone from the polymeric microparticles was measured as described in Exhibit B.

6. The *in vitro* release kinetics shown in Exhibit C demonstrate that far greater release of prednisone occurs with the microparticles made with both a hydrophobic compound and a pore forming agent as disclosed in our patent application than with the microparticles without the hydrophobic compound and made without a pore forming agent or the microparticles made with a hydrophobic compound but without a pore forming agent as disclosed in Hanes et al..

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements are made with the knowledge that willful false statements are

punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: May 14, 2001

Howard Bernstein

Howard Bernstein, M.D. Ph.D.

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Exhibit A: Production of Microparticles

Materials

The following materials were purchased from Spectrum Chemicals, Gardena, CA: prednisone and ammonium bicarbonate. PLGA (50:50 , Molecular weight approximately 40,000 Daltons) was purchased from BI Chemicals, Inc., Wallingford, CT. Methylene chloride was purchased from EM Science, Gibbstown, NJ. DAPC was purchased from Avanti Polar Lipids, Alabaster, AL. All emulsions were generated using a Virtis IQ² homogenizer (Virtis, Gardiner, NY) and spray dried on a benchtop spray dryer using an air atomizing nozzle.

i) Prednisone PLGA Microspheres: Batch 9919-163

A prednisone-loaded organic solution was prepared by dissolving 6 g of PLGA and 0.6 g of prednisone in 200 ml of methylene chloride at 37°C. The resulting solution was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas. Spray drying conditions were as follows: 20 ml/min solution flow rate, 40 L/min atomization gas rate, 60 kg/hr drying gas rate, and 20°C outlet temperature.

ii) Prednisone PLGA Microspheres Containing DAPC: Batch 9919-164

A prednisone-loaded organic solution was prepared by dissolving 6 g of PLGA, 0.6 g of prednisone, and 0.36 g of DAPC in 200 ml of methylene chloride at 37°C. The resulting solution was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas. Spray drying conditions were as follows: 20 ml/min solution flow rate, 60 L/min atomization gas rate, 60 kg/hr drying gas rate, and 20°C outlet temperature.

iii) Prednisone PLGA Microspheres Containing the Hydrophobic Compound DAPC and Produced with A Pore Forming Agent: Batch 9919-166

A prednisone-loaded organic solution was prepared by dissolving 6 g of PLGA, 0.6 g of prednisone, and 0.36 g of DAPC in 200 ml of methylene chloride at 37°C. An aqueous solution was prepared by dissolving 3.6 g of ammonium bicarbonate in 20 ml of DI water at 37°C. The aqueous solution was added to the organic solution (phase ratio 1:10) and homogenized for 5 minutes at 16,000 RPM in a 500 ml round-bottomed homogenization flask using a Virtis IQ² homogenizer. The resulting emulsion was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas. Spray drying conditions were as follows:

20 ml/min solution flow rate, 60 L/min atomization gas rate, 60 kg/hr drying gas rate, and 20°C outlet temperature.

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Exhibit B: Method For Determining The Release Kinetics of Prednisone from PLGA Microspheres

The release kinetics of Prednisone from the microparticles were conducted in PBS (phosphate buffered saline) containing 0.08% Tween 80 (T80/PBS) in 50 mL polypropylene conical tubes filled to a volume of 40 mL. The tubes were vortexed 1 minute, and then were placed in a 37°C incubator, and were rotated with gentle inversion. The rotator was a Glas-Col (Cat. # 099A RD4512) set to 20%. Microsphere samples were suspended at a theoretical maximum concentration of 20 µg prednisone/mL. At each time-point, samples were removed via pipet and filtered through 0.22 µm CA syringe filtered. Samples were analyzed via UV-vis spectroscopy (Hewlett Packard Model 8453) for prednisone at 244 nm.

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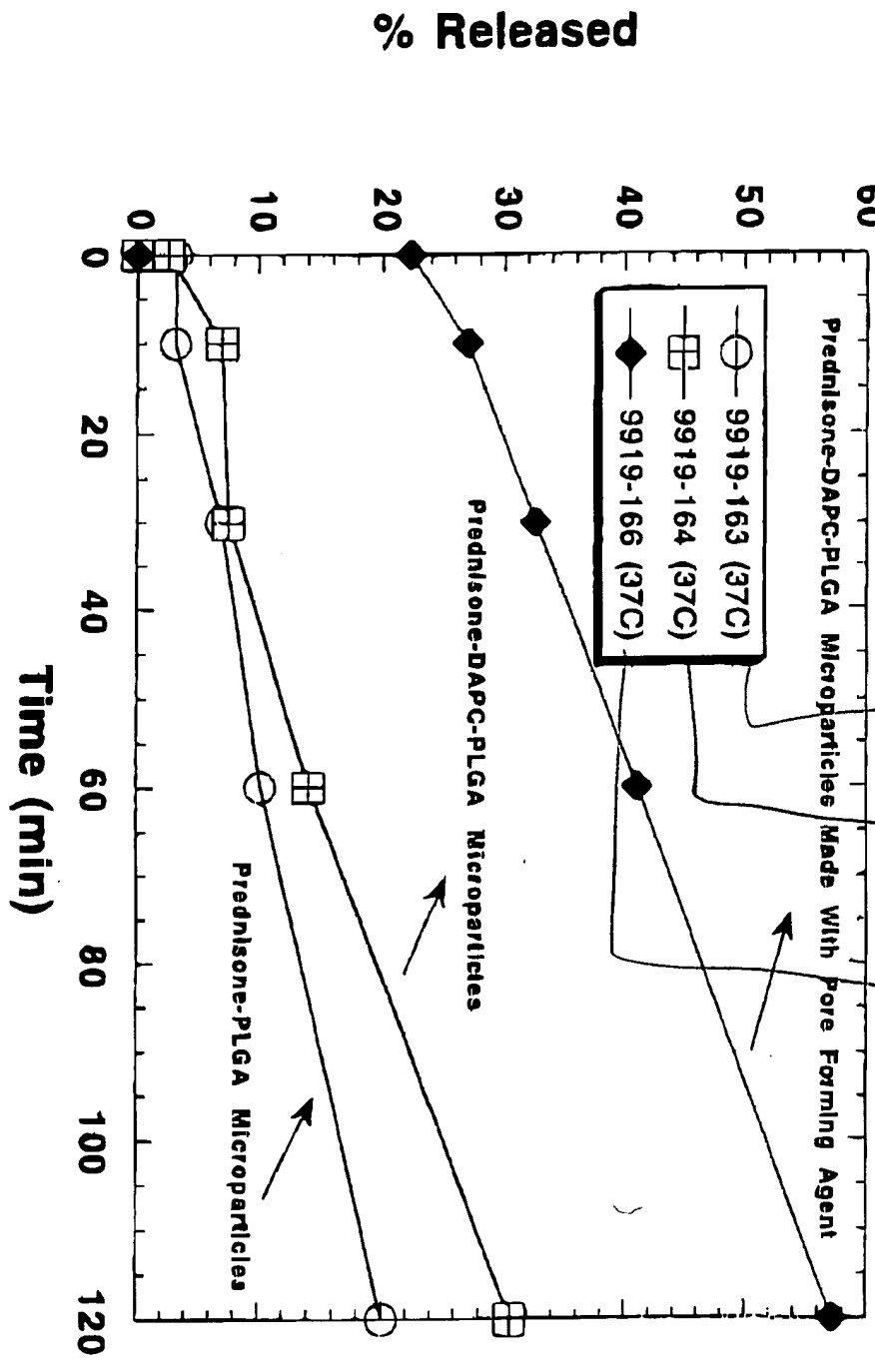
Exhibit C: Release Kinetics of Prednisone from PLGA Microspheres



SOLV, NO DAPC

SOLV

PORE FORMER

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Employment

10/94- Acusphere Inc., Cambridge, MA.

1/2000 Senior Vice President, Research and Development
Overseeing the Research and Development of Intravenously Administered Diagnostic Contrast Agents and Drug Delivery Systems. Technical and Managerial Leadership of 20 Scientists including with an Annual Budget of $10,000,000

10/94-1/2000 Vice President, Research and Development
Overseeing the Research and Development of Intravenously Administered Diagnostic Contrast Agents and Drug Delivery Systems. Technical and Managerial Leadership of 20 Scientists including with an Annual Budget of $6,000,000.

11/92 to 9/94 Alkermes Inc., Cambridge, MA

Vice President, Pharmaceutical Development
Technical and Managerial Leadership of 25 Scientists including 10 Ph.D.'s with an Annual Budget of $8,000,000. Overseeing the Internal and External Development of all Parental and Oral Dosage Forms including Proteins, Peptides, and Generic Drugs.

10/88 to 11/92 Enzytech Inc., Cambridge, MA

9/91 to 11/92 **Vice President, Research**
Technical and Managerial Leadership of 40 Scientists including 10 Ph.D.'s with a Total Annual Budget of $10,000,000. Overseeing the Research and Preclinical Development of Parenteral and Oral Drug Delivery Systems for Protein, Peptide and Generic Drugs. Responsible for Analytical Chemistry, Bioanalytical Chemistry, Formulations, Pharmacology, Pharmacokinetics, Process Development and Toxicology.

3/91 to 9/91 **Group Director**
Director of the Parenteral Systems Research & Development Program and the Oral Delivery of Proteins/Peptides Research Program. Responsible for Analytical Chemistry, Bioanalytical Chemistry, Formulations, Pharmacology and Pharmacokinetics. Managed a group of 6 Ph.D.'s and 15 BS/MS.

10/90-3/91 **Associate Principal Investigator**
Director of the Oral Delivery of Proteins/Peptides Research Program. Project Leader for Injectible Microsphere Systems. Set up Analytical Chemistry, Bioanalytical Chemistry, Formulations and Pharmacology Groups. Managed group of 4 Ph.D.'s and 8 BS/MS.

10/88-10/90 **Senior Research Scientist**
Project Leader for Research Program on Injectible PLGA Depot systems. Set up Research Program for the Delivery of Peptides and Proteins by the Oral Route and Co-Invented Novel Microparticulate Delivery System. Managed a group of 2 Ph.D.'s and 4 BS/MS.

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1997	Fellow of American Institute for Medical and Biological Engineering
1990	Controlled Release Society. Outstanding Pharmaceutical Paper of the Year.
1983-85	Edgar Poitras Fellowship, MIT.
1979-83	Medical Research Council of Canada Scholarship.
1979	1967 Centennial Scholarship, National Science and Engineering Research Council of Canada.
1979	American Chemical Society Merit Award.

Professional Affiliations

American Association for the Advancement of Science (AAAS)
American Association of Pharmaceutical Sciences (AAPS)
American Chemical Society (ACS)
American Medical Association (AMA)
Controlled Release Society (CRS)
Massachusetts Medical Society (MMS)
Parenteral Drug Association (PDA)
Sigma Xi

Education

1989	**Harvard Medical School**, Boston, MA. Doctor of Medicine.
1985	**Massachusetts Institute of Technology**, Cambridge, MA. Ph.D. in Chemical Engineering.
1982	**Massachusetts Institute of Technology**, Cambridge, MA. Master of Science in Chemical Engineering.
1979	**McGill University**, Montreal, Canada. Bachelor of Chemical Engineering with Great Distinction.

Publications

1) Howard Bernstein and Robert Langer, "Design of an Immobilized Enzyme Reactor for Removing Heparin at the Termination of Extracorporeal Therapy.", Proceedings of the American Chemical Society 51, 204-207, (1984).

2) Victor C. Yang, Robert Linhardt, Howard Bernstein, Charles L. Cooney, and Robert Langer," Purification and Characterization of Heparinase from *Flavobacterium Heparinum*.", The Journal of Biological Chemistry 260, 1849-1857, (1985).

3) Robert Langer, Howard Bernstein, Annette Larsen, Victor C. Yang, David Tapper and Dennis Lund, "An Enzymatic Approach to Anticoagulation Control." ASAIO Journal 8, 213-215. (1985).

4) Howard Bernstein, Victor C. Yang and Robert Langer, "An Immobilized Enzyme Reactor for Extracorporeal Dehaparinization", in **New Aspects in Extracorporeal Detoxification**, p22, Chmiel and E. Streicher, 3rd Tutzing Symposium on Engineering in Medicine, Lake Starnberg, West Germany.

5) Victor C. Yang, Howard Bernstein, Charles Cooney and Robert Langer, "A Novel Approach for Neutralizing Low Molecular Weight Heparin Fragments.", Fed. Proc. 44, 1846, (1985).

6) Howard Bernstein, Jeffrey Atherton and William Deen, "Axial Heterogeneity of Proximal Bicarbonate Reabsorption." Biophysical Journal 50(2), 239, (1986).

7) Victor C. Yang, Howard Bernstein, Charles Cooney and Robert Langer, "A Novel Approach for Neutralizing the Anticoagulability of the Low Molecular Weight Heparins.", Thrombosis Research 44, 599-610, (1986).

8) Howard Bernstein and Robert Langer, "An Immobilized Enzyme System for Heparin Removal.", in **Artificial Organs: The W.F. Kolff Festschrift** (Ed. J. Andrade), pp 333-342, VCH Publishers, (1987).

9) Howard Bernstein, Victor C. Yang and Robert Langer, "The Distribution of Heparinase Covalently Immobilized to Agarose: Experimental and Theoretical Studies.", Biotech. Bioeng. 30, 196-207, (1987).

10) Howard Bernstein, Victor C. Yang and Robert Langer. "Immobilized Heparinase: an *In Vitro* Reactor Study.", Biotech Bioeng. 30, 239-250, (1987).

11) Victor C. Yang, Howard Bernstein and Robert Langer, "Large Scale Purification of Catalytically Pure Heparinase.", Biotech Progress 3, 339-353, (1987).

12) Howard Bernstein, Dennis Lund, Mohinder Randawa, Victor C. Yang, Bill Harmon and Robert Langer, "Extracorporeal Enzymatic Heparin Removal: Use in a Sheep Dialysis Model.", Kidney International 32, 452-463, (1987).

13) Victor C. Yang, Howard Bernstein, Charles Cooney and Robert Langer, "Large Scale Preparation of Contamination Free Heparinase.", Appl. Biochem. Biotech. 16, 35-50, (1987).

14) Howard Bernstein, Victor C. Yang and Robert Langer, "A Systematic Investigation of Heparinase Immobilization.", Applied Biochem. Biotech. 17, 129-143, (1988).

15) Howard Bernstein, Victor C. Yang, Charles Cooney and Robert Langer, "An Immobilized Heparinase System for Blood Deheparinization.", Methods in Enzymology, (K. Mosbach, ed.), Academic Press, 137, 515-529, 1988.

16) Howard Bernstein and Robert Langer, "Modeling of an Immobilized Enzyme Reactor *Ex Vivo*.", Proc. Nat. Acad. Sci., 85 8751-8755, (1988).

17) Victor C. Yang, Howard Bernstein, and Robert Langer, "Heparinase Immobilization and Optimization.", Enzyme Engineering 9, 515-520, (1989).

18) Gordana Vunjak-Novakovic, Lisa Freed, Howard Bernstein, Shiva Ayyadurai, Robert Langer and Charles Cooney, "A Fluid Dynamic Study of the Enzymatic Fluidized Bed Reactor for Blood Deheparinization.", **Proceedings of the 6th International Conference of Fluidization**, Banff, Alberta, (1989).

19) Robert Langer, Howard Bernstein, Larry Brown and Linda Cima, "Medical Reactors.", Chem. Eng. Sci. 45, 1967-1978, (1990).

20) Smadar Cohen, Howard Bernstein, Marie Chow and Robert Langer, "Liposome-Based Formulations as Adjuvants for Peptide Vaccines.", **Proc. Intern. Symp. Control. Rel. Bioact. Mater. 17**, 210-211, (1990)

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22) Edith Mathiowitz, Howard Bernstein, Steve Giannos, Phillipe Dor and Robert Langer, "Polyanhydride Microspheres: IV. Morphology and Characterization of Systems Made by Spray Drying.", **J. Appl. Polym. Sci** 45, 125-134, (1992).

23) Sang Do Yeo, Pablo Debenedetti and Howard Bernstein, "Production of Protein Particles using RESS.", **Biotech. Bioeng.** 41, 341-346 (1993).

24) Yan Zhang, Stephen Zale, Laura Sawyer and Howard Bernstein, "Effect of Metal Salts on PLGA Degradation", **Proc. Intern. Symp. Control. Rel. Bioact. Mater. 22**, 83-84 (1995).

25) Yan Zhang, Stephen Zale, Laura Sawyer and Howard Bernstein, "Effect of Metal Salts on PLGA Hydrolysis", **J. Biomedical Materials Research, 34**, 531-538. (1997).

Patents

1) Howard Bernstein and Robert Langer. Fluidized Extracorporeal Reactors Containing Immobilized Species for Blood Detoxification, U.S. Patent 4,863,611.

2) Edith Mathiowitz, Howard Bernstein, Eric Morrell and Kristen Schwaller, "Method for Producing Protein Microspheres, U.S. Patent 5,271,961.

3) Howard Bernstein, Eric Morrel, Edith Mathiowitz and Tom Beck, "Methods for Using Protein Microspheres", U.S. Patent 5,679,377.

4) Amin Khan and Howard Bernstein, "Controlled Release Formulations for ACTH", U.S. Patent 5,413,797.

5) Funmi Johnson, Medha Ganmuhki, Howard Bernstein, Henry Auer, and Amin Khan, " Composition for Sustained Release of Human Growth Hormone", U.S. Patent 5,654,010.

6) Funmi Johnson, Medha Ganmuhki, Howard Bernstein, Henry Auer, and Amin Khan, " Composition for Sustained Release of Human Growth Hormone", U.S. Patent 5,667,808.

7) Howard Bernstein, Edith Mathiowitz, Eric Morrel and Avram Brickner, "Erythropoietin Containing Prolamine Drug Delivery Systems", U.S. Patent pending.

8) Mary DiBiase and Howard Bernstein, "Oral Dosage form of dDAVP ", U.S. Patent pending.

9) Howard Bernstein, Yan Zhang, Mark Tracy and Amin Khan, "Modulated Release from Biocompatible Polymers", U.S. Patent 5,656,297.

10) Mark Tracy, Howard Bernstein and Amin Khan, "Composition and Method for the Controlled Release of Metal Cation Stabilized Interferon ", U.S. Patent 5,711,968.

11) Mark Tracy, Howard Bernstein, Henry Auer, Amin Khan, Paul Burke, Funmi Johnson, and Stephen Zale, " Device for the Sustained Release of Aggregation Stabilized Biologically Active Agent", U.S. Patent pending.

12) Stephen Zale, Paul Burke, Howard Bernstein, and Avram Brickner, "Composition for Sustained Release of Non-Aggregated Erythropoietin", U.S. Patent 5,674,534.

13) Stephen Zale, Paul Burke, Howard Bernstein, and Avram Brickner, "Composition for Sustained Release of Non-Aggregated Erythropoietin", U.S. Patent 5,716,644.

14) Howard Bernstein, Julie Straub, Henry Brush, and Richard Wing, "Synthetic Polymeric Microparticles Containing Fluorinated Gases for Diagnostic Imaging", U.S. Patent 5,611,344.

15) Julie Straub, Edith Mathiowitz, Howard Bernstein and Henry Brush, "Method For Making Porous Microparticles by Spray Drying", U.S. Patent 5,853,698.

16) Howard Bernstein, Julie Straub, Henry Brush, and Charles Church, "Polymer-Lipid Microencapsulated Gases for use as Imaging Agents", U.S. Patent 5.837,221.

17) Charles Church, Howard Bernstein, Julie Straub and Henry Brush, " Low Attenuating Ultrasound Contrast Media", U.S. Patent 6,045,777.

18) Funmi Johnson, Medha Ganmuhki, Howard Bernstein, Henry Auer, and Amin Khan, " Composition for Sustained Release of Human Growth Hormone", U.S. Patent 5,891,478.

19) Howard Bernstein, Yan Zhang, Mark Tracy and Amin Khan, "Modulated Release from Biocompatible Polymers". U.S. Patent 5,912,015.

20) Funmi Johnson, Medha Ganmuhki, Howard Bernstein, Henry Auer, and Amin Khan, " Composition for Sustained Release of Human Growth Hormone", U.S. Patent 6,051,259.

21) Howard Bernstein, Julie Straub, Henry Brush, and Richard Wing, "Synthetic Polymeric Microparticles Containing Fluorinated Gases for Diagnostic Imaging", U.S. Patent 6,132,699.

22) Mark Tracy, Howard Bernstein and Amin Khan, "Controlled Release of Metal Cation Stabilized Interferon ", U.S. Patent 6,165,508.

23) D. Chickering, H. Bernstein, M. Keegan, G. Randall and J. Straub, " Spray Drying Apparatus and Methods of Use". U.S. Patent 6,223,455.

Books Edited

1) "Biomaterials for Drug and Cell Delivery" edited by Antonios Mikos, Regina Murphy, Howard Bernstein and Nicholas Peppas", Material Research Society Symposium Proceedings, 1994.

2) "Microparticulates-Preparation, Characterization and Application to Medicine", edited by Howard Bernstein and Smadar Cohen, Marcel Dekker, (1995).

Conference Sessions Chaired

1) "The Use of Immobilized Species for Medical Appellations", **American Institute of Chemical Engineering**, November 12, 1989, San Francisco, CA.

2) "Drug Delivery of Macromolecules", **American Chemical Society**, April 5, 1992, San Francisco, CA.

3) "Protein Peptide Delivery Systems" **Controlled Release Society**, July 23, 1992, Orlando FL.

4) "Biomaterials for Drug and Cell Delivery", **Materials Research Society**, Dec. 1993, Boston, MA

Invited Presentations

1) "Novel Drug Delivery Systems for Proteins and Peptides", **Second U.S.-Japan Symposium on Drug Delivery Systems**, Maui, Hawaii, December 1993.

2) "Parenteral Delivery of Labile Macromolecules", **XI Congress of the International Society for Artificial Cells, Blood Cells and Immobilization Biotechnology**, Boston, MA, July 1994.

Abstracts

1) Howard Bernstein and Robert Langer, "Design of an Immobilized Enzyme Reactor for Removing Heparin at the Termination of Extracorporeal Therapy", **American Chemical Society**, Philadelphia, PA, August 1984.

2) Howard Bernstein, Victor C. Yang, Mohinder Randhawa and Robert Langer, "A Reactor for Removing Heparin at the Termination of Extracorporeal Therapy", **American Chemical Society**, Miami, FL, April 1985.

3) Howard Bernstein, Victor C. Yang, Mohinder Randhawa and Robert Langer, "An Immobilized Enzyme Reactor for Extracorporeal Deheparinization", **3rd Tutzing Symposium on Chemical Engineering in Medicine**, Munich, West Germany, September 1985.

4) Howard Bernstein and Robert Langer, "An Ex Vivo Model for Heparin Removal in Blood", **Biomaterials Conference on Drug Delivery**, Cambridge, England, July 1986.

5) Victor C. Yang, Howard Bernstein, Mohinder Randhawa and Robert Langer, "A Novel Approach for Diminishing Bleeding Risk using Low Molecular Weight Heparins in Extracorporeal Therapy", **ASAIO**, New York, May 1987.

6) Edith Mathiowitz, Howard Bernstein and Robert Langer, "Morphological Approaches to Determine Surface Erosion", **Controlled Release Society**, Chicago, Illinois, 1989.

7) Gordana Vunjak-Novakovic, Lisa Freed, Howard Bernstein, Shiva Ayyadurai, Robert Langer and Charles Cooney, "A Fluid Dynamic Study of the Enzymatic Fluidized Bed Reactor for Blood Deheparinization.", **6th International Conference on Fluidization**, Banff, Alberta, (1989).

8) Howard Bernstein, Gordana Vunjak-Novakovic and Lisa Freed, "A Comparative Modeling Study of Immobilized Heparinase Reactors", **American Chemical Society**, Boston, MA, April 1990.

9) Smadar Cohen, Howard Bernstein, Marie Chow and Robert Langer, "Liposome-Based Formulations as Adjuvants for Peptide Vaccines", **Controlled Release Society**, Reno, Nevada, 1990.

10) Edith Mathiowitz, Donald Chickering, Mary DiBiase, Howard Bernstein and Marian Sherman, "GI Transit of Hydrophobic Protein Microspheres", **Controlled Release Society**, Nice, France, 1994.